REMARKS

The Examiner's attention to the present application is noted with appreciation.

Introduction. Applicant has amended claim 2 to incorporate the limitations of claims 7 and 8, such that the metal ion-binding domain is complexed with a metal ion selected from the group consisting of rhenium and technetium, and where the peptide is substantially more specific for a melanocortin receptor when it is complexed with a metal ion than when it is not. The only references cited against claim 7 (or its corollary claim 20) are the Shi et al. abstract and the Giblin et al. article. With respect to the Shi et al. abstract, Applicant submits a declaration pursuant to 37 CFR 1.132, and further argues that Shi et al. is not properly prior art. With respect to the Giblin et al. article, Applicant argues, as set forth below, that Giblin et al. does not anticipate because it does not teach every element of the claim, and further because it is not properly prior art. Accordingly, Applicant submits that the claims as amended are allowable over the prior art of record.

It is noted that claims 31, 39 and 40, limited to the elected species, are objected to as being dependent upon a rejected based claim, but would be allowable if rewritten in independent form.

Objection To Claim 8. In paragraph numbered 2, claim 8 is rejected as being indefinite. The claim has been canceled, with the substantive limitation thereof, amended to correct the error, incorporated into claim 2.

Entitlement Under 35 USC § 119(e) To Benefit Of Filing Date Of Provisional Application 60/148,994. For the reasons set forth in the previous response, Applicants respectfully traverses the statement in paragraph 3 of the Office Action that the provisional application "does not disclose peptides in general in which the biological-function domain is co-extensive with at least a portion of the metal ion-binding domain." This is, of course, the critical limitation of claim 2 of the instant application.

At paragraph numbered 8, on pages 5-7, the Examiner states three objections: first, the quoted paragraph at page 16, first paragraph is asserted to be a "species" that does not provide written descriptive support for a genus claimed in a child application. Second, it appears that the reverse turn structures is only a "species" of the metal ion-binding domain, and a species does not provide written descriptive support for a genus. Finally, three specific examples do not provide "written descriptive support" for compounds embraced by the elected species.

As stated at page 11 of the provisional application, last paragraph, " a peptide ... is folded to form a kind of reverse turn upon its complexation with a metal ion." Thus the constructs of the invention form a reverse turn structure. See also pages 74 to 84 of the provisional application.

Second, the text at pages 15 to 16 of the provisional application, and quoted in the previous response, provide both a specific example (the structure of the recited formula) **and** a general description that is not limited to the specific example. The statement that "a library is provided in which the metal ion-binding amino acid sequence in the peptides forms a reverse turn structure upon complexation with a metal ion, with the library constructed such that side chains of amino acids within the metal ion-binding sequence are varied..." describes generically peptides in which at least a portion of the biological-function domain is co-extensive with at least a portion of the metal ion-binding domain. As the provisional application teaches, the side chains are varied in order to change the biological binding.

Of equal importance is the fact that in <u>every one</u> of the literally hundreds of different compounds disclosed in Table 1 of provisional application at pages 25 to 41 "at least a portion of said biological-function domain is co-extensive with at least a portion of the metal ion-binding domain." This is necessary so because in <u>every</u> instance at least one amino acid immediately adjacent the Cys residue which necessarily forms part of the metal ion binding domain is part of the biological-function domain -- it is a Trp, Phe, Arg, or His (i.e., a component of the melanocortin His-Phe-Arg-Trp core sequence) or a mimic thereof, such as Nal. See also Example 1, page 43 of the provisional, disclosing a template in which alpha amines of D-Phe and Arg form part of the metal ion-binding domain. See also the example on page

45, disclosing a generic formula in which the "Aaa" and "Bbb" components necessarily contribute to metal ion binding and are selected such as to be part of the biological-function domain (i.e., 2-Nal, Phe, Trp, Tyr or Ala). Finally, the entire last portion of the provisional application, pages 70-84, discusses and describes constructs in which at least a portion of the biological-function domain is co-extensive with at least a portion of the metal ion-binding domain. See, e.g., page 72, stating "[b]iological affinity and specificity in these templates may be induced upon decorating them with appropriate functional groups." The templates are the metal ion-binding regions (e.g., a "metal ion complexed metallo-peptide template."). See also page 78 (other generic structures with R_3 and R_2 groups); page 79, stereoviews showing metal ion-complexed peptides with side chains of the "metal ion-binding domain" in biologically active positions, overlapping with Beta-II' turns; page, 80, same; page 81, extended chains; page 82, beta sheets; and page 83, helix turns.

The refusal to accord the benefit of the filing date of the provisional is largely based on the fact that the exact words of the present claim do not appear in the provisional. However, this is not the test. As the MPEP provides, "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." MPEP § 2163.02. Similarly, as the MPEP also provides, "newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." MPEP § 2163. Thus the description requirement can be supported by either implicit or inherent disclosure, and there is no requirement that the "same terms" be used in order to satisfy the description requirement. Additionally, as case law and the MPEP make clear, an applicant shows possession of the claimed invention by describing it "using such descriptive means as words, structures, figures, diagrams and formulas." MPEP §§ 2163, 2163.02; *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

The inherent and implicit disclosure in the provisional application is that a class of compounds is disclosed in which at least a portion of the biological-function domain is co-extensive with at least a portion of the metal ion-binding domain. The presence of literally hundreds of example, each of which meet this

definition, combined with a number of more general formulas, provide sufficient written description to accord a priority date as of the provisional filing date as to claim 2.

Rejections Based on Sharma et al., Fabris et al. and Shi et al. The rejection based on Sharma et al. was withdrawn in the last Office Action. The rejection based on Fabris et al. is not asserted as to claims 7 or 20 (rhenium or technetium). Claim 2 is amended to include the limitation of claim 7, and accordingly distinguishes from Fabris et al. With respect to the Shi et al. reference, a declaration pursuant to 37 CFR 1.132 is submitted herewith, establishing that the inventors are properly named, and that the two additional authors of the Shi et al. reference, C. Blood and A. Shadiack, were conducting biological assays and tests on compounds conceived and made by the named inventors.

Rejection Based on Giblin et al. In paragraph numbered 7, the rejection of claims 2, 7, 8, 18, 20, 26-29, and 33 as being anticipated by Giblin et al. is maintained. The rejection is traversed.

Applicants stated in the prior response that the Giblin et al. reference "specifically teaches away from a biological-function domain which is co-extensive with at least a portion of a metal ion-binding domain, and teaches away from the compounds being more specific when in the complexed state in comparison to the uncomplexed state." Applicants apologize if this language was confusing. Applicants mean by "teaches away" that the Giblin et al. references fails to teach every element of the claim. This is not an obviousness argument pursuant to section 103, but is rather an anticipation argument pursuant to section 102.

In paragraph numbered 7 of the Office Action (page 5), it is stated that the Giblin peptides "are deemed inherently to have a determined biological-function domain, to have a biological-function domain which is co-extensive with at least a portion of a metal ion-binding domain, and to be substantially more specific for one or more melanocortin receptors when in the complexed state in comparison to the uncomplexed state, to the same extent claimed by Applicants." However, the disclosure of Giblin et al.

itself specifically and in detail provides evidence that the claimed peptides of the present invention are unobviously different than the peptides of the Giblin et al. reference.

Giblin describes and discloses only cyclic peptides cylicized through cysteine residues. There are two peptides discussed at length in the paper, NAc-Cys-Glu-His-D-Phe-Arg-Trp-Cys-Lys-Pro-Val-NH_2 and NAc-Cys-Cys-Glu-His-D-Phe-Arg-Trp-Cys-Lys-Pro-Val-NH_2 (see page 12815, first column, first sentence under heading "Synthesis and Purification of Peptide-Metal Complexes"). The first, containing two Cys residues, is called "cyclic α-MSH analog ($Cys^{4,10}$, D-Phe^7)-α-MSH_{4-13} (APOMSH)" (see page 12815, second column, under heading "Metal-Binding Site Design"), and was described as having been invented in 1985 (reference 24 in the Giblin paper). When labeled with rhenium, the APOMSH peptide is called "ReMSH." The second peptide was evidently developed by Giblin et al., and is referred to as "CCMSH" when not labeled with a metal ion, and "ReCCMSH" when labeled with rhenium. This peptide contains three cysteine residues, and is sometimes referred to as "$Cys^{3,4,10}$, D-Phe^7-α-MSH_{3-13}" (see page 12814, "Abbreviations").

With respect to the "APOMSH" and "ReMSH" peptides, Giblin et al. states that the rhenium labeled peptides was substantially less specific for one or more melanocortin receptors. See page 12816, second column, first full sentence:

> The K_i for the ReMSH complex was 6.6×10^{-8}, which reflected an apparent receptor binding affinity reduction to 1/100 that of APOMSH ($K_i = 6.8 \times 10^{-10}$). Therefore, it appeared that the presence of the Re(V)O core or its effect on the solution structure of ReMSH significantly reduced the molecule's receptor affinity.

Thus the ReMSH compound clearly and explicitly fails to meet the limitation of claim 2 as amended.

The second embodiment disclosed by Giblin et al., the CCMSH variant, has an additional N-terminal Cys residue. As Giblin et al. states, at 12816, second column, bridging 12817, first column:

> It was hypothesized that inclusion of this additional thiolate would drive the metal-coordination sphere away from the His-D-Phe-Arg-Trp core sequence by taking advantage of the increased affinity of Re and Tc for sulfur donor atoms over nitrogen. NMR characterization of this ReCCMSH complex indicated that only a single amide proton resonance had been lost on Re complexation. The single amide ^1H resonance lost in ReCCMSH was assigned to Cys-4.

Thus it was clearly intended, by express design, that the "metal ion-binding domain" be distinct and separate from the biological-function (His-DPhe-Arg-Trp) domain -- and accordingly the limitation of claim 2 that "at least a portion of said biological-function domain is co-extensive with at least a portion of the metal ion-binding domain" is neither taught nor disclosed by Giblin et al. This is clearly seen in FIG. 1 of Giblin et al. (page 12816) which shows the rhenium coordination side in the ReCCMSH molecule separate, distinct and distal from the His-DPhe-Arg-Trp domain. At most, the 1998 disclosure by Giblin et al. is simply a variant akin to Example 44 of U.S. Patent 5,891,418, which has been withdrawn as a prior art reference.

Giblin et al. discusses, in passing, a third embodiment, described as inserting a "Gly" spacer residue between the Trp and C-terminus Cys. However, this was also largely inactive, and here too the biological-function (His-DPhe-Arg-Trp) domain was not co-extensive with at least a portion of a metal ion-binding domain.

The entire focus and disclosure of the Giblin et al. reference is encapsulated at 12815, second column, under the heading "Metal-Binding Site Design", in which is it is stated that "[t]he metal-binding site must be engineered so that metal coordination does not disrupt the biologically active conformation of the molecule." This is different from Applicants' invention, in which it is an object to design a molecule such that the biological-function domain is "co-extensive" with at least a portion of the metal ion-binding domain, such that there results a conformationally constrained and biologically active structure upon metal ion complexation. Thus properly understood Giblin et al. does not anticipate the invention as now claimed because the reference does not "teach every element" of the claimed invention. Giblin et al. itself specifically and in detail provides evidence that the claimed peptides of the present invention are unobviously different than the peptides of the Giblin et al.

Conclusion. In view of the above amendments and remarks, it is respectfully submitted that all grounds of rejection and objection have been avoided and/or traversed. It is believed that the case is now in condition for allowance and same is respectfully requested.

If any issues remain, or if the Examiner believes that prosecution of this application might be expedited by discussion of the issues, the Examiner is cordially invited to telephone the undersigned attorney for Applicant at the telephone number listed below.

Respectfully submitted,

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